



Everaert, K., Hervé, F., Bosch, R., Dmochowski, R., Drake, M., Hashim, H., Chapple, C., Van Kerrebroeck, P., Mourad, S., Abrams, P., & Wein, A. (2019). International Continence Society consensus on the diagnosis and treatment of nocturia. *Neurourology and Urodynamics*, 38(2), 478-498. <https://doi.org/10.1002/nau.23939>

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# International Continence Society consensus on the diagnosis and treatment of nocturia

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<https://doi.org/10.1002/nau.23939>

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Editorial assistance was provided by Caroline Loat, PhD.

## Abstract

## Introduction

Patients with nocturia have to face many hurdles before being diagnosed and treated properly. The aim of this paper is to: summarize the nocturia patient pathway, explore how nocturia is diagnosed and treated in the real world and use the Delphi method to develop a practical algorithm with a focus on what steps need to be taken before prescribing desmopressin.

## Methods

Evidence comes from existing guidelines (Google, PubMed), International Consultation on Incontinence-Research Society (ICI-RS) 2017, prescribing information and a Delphi panel (3 rounds). The International Continence Society initiated this study, the authors represent the ICI-RS, European Association of Urology, and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU).

## Results

Diagnostic packages: consensus on, history taking for all causalities, intake diary (fluid, food) and bladder diary, not for its duration. Pelvic (women) or rectal (men) examination, prostate-specific antigen, serum sodium check (SSC), renal function, endocrine screening: when judged necessary. Timing or empty stomach when SSC is not important. Therapeutic packages: the safe candidates for desmopressin can be phenotyped as no polydipsia, heart/kidney failure, severe leg edema or obstructive sleep apnea syndrome. Lifestyle interventions may be useful. Initiating desmopressin: risk management consensus on three clinical pictures.

Follow-up of desmopressin therapy: there was consensus on SSC day 3 to 7, and at 1 month. Stop therapy if SSC is <130 mmol/L regardless of symptoms. Stop if SSC is 130 to 135 mmol/L with symptoms of hyponatremia.

## Conclusion

A summary of the nocturia patient pathway across different medical specialists is useful in the visualization and phenotyping of patients for diagnosis and therapy. By summarizing basic knowledge of desmopressin, we aim to ease its initiation and shorten the patient journey for nocturia.

## 1 INTRODUCTION

Nocturia was defined in 2002 as a complaint that the individual has to wake at night one or more times to void.<sup>1</sup> It affects a high proportion of adults.<sup>2</sup> Nevertheless, for a long time, the symptom received very little specific research attention as it was considered just one of a number of lower urinary tract symptoms (LUTS) indicating overactive bladder (OAB) or benign prostatic obstruction (BPO). In recent years, however, there has been growing recognition that it is a specific symptom in its own right, with wide-ranging pathophysiology (including blood pressure changes, cardiac dysfunction, fluid shift into the lower limbs, polyuria, sleep apnea, insomnia, pharmacotherapy, and polypharmacy). Furthermore, it is associated with significant negative outcomes in terms of patient health, sleep, and quality of life. Yet there is no consensus on how to identify and manage nocturia patients for the best possible outcomes.

During the 2017 meeting of the International Consultation on Incontinence-Research Society (ICI-RS) in Bristol, a nocturia think-tank discussed how to study the gaps in our knowledge to develop a practical patient-oriented diagnostic and therapeutic algorithm for nocturia.<sup>3</sup> It was obvious that the many and varied causes of the condition are underdiagnosed and that many clinicians of different disciplines see patients with nocturia without paying specific attention to diagnosing and treating their excessive nocturnal voiding.

Nocturia guidelines are mainly hidden within broader LUTS guidelines because nocturia has historically been linked primarily to OAB and BPO, even though its main cause is nocturnal polyuria (NP).<sup>5</sup> A one-year delay between onset of LUTS symptoms and consultation of a

medical professional has been reported.<sup>6</sup> Patients with nocturia are treated by healthcare providers from numerous different disciplines because nocturia is prevalent in many other conditions, such as cardiovascular disease, diabetes, and OAB. However, the specific condition of nocturia is ignored by most specialities, and only rarely does it improve with treatment of other underlying conditions. Different medical disciplines diagnose and treat nocturia or its underlying diseases using their own guidelines and recommendations based on levels of evidence available from prior research and literature. Diagnostic and therapeutic “packages” from each discipline are helpful to visualize the approach to nocturia that is taken in clinical practice.

No single treatment can effectively treat nocturia in all contexts. However, desmopressin is the only evidence-based pharmaceutical therapy for nocturia.<sup>7</sup> Despite this, the breadth of its use in clinical practice is limited.<sup>6, 8</sup> Patients with nocturia have to face many hurdles before being diagnosed properly and treated with desmopressin, instead of OAB/BPO medication.<sup>6</sup> Potential reasons for this, besides side effects, are the limited knowledge of clinicians regarding the drug and how to use it, and anxiety about safety, regardless of the evidence that with the available low-dose formulations, hyponatremia is extremely rare, even in older patients.<sup>9, 10</sup> There is a clear need for a summary of the available information and a simple algorithm on how desmopressin should be used in adults with nocturia.

The aim of this paper, based on the International Continence Society’s (ICS) 2002 document,<sup>1</sup> is to:

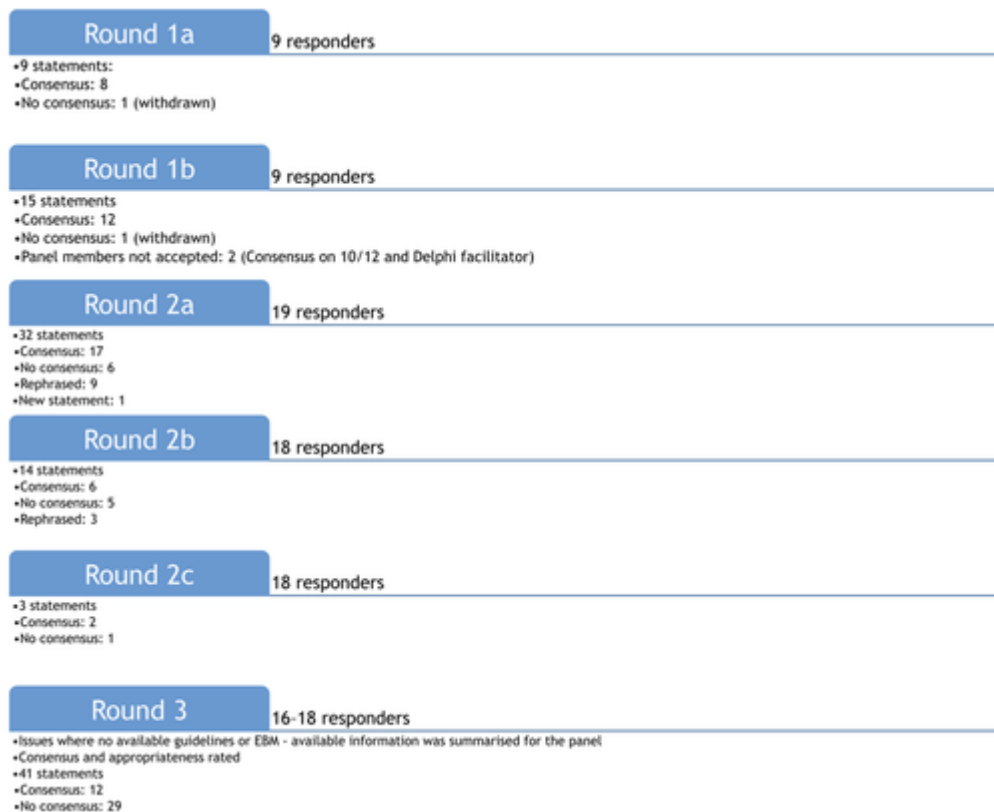
- 1) Summarize the nocturia patient pathway.
- 2) Explore how nocturia is diagnosed and treated in the real world.
- 3) Use the Delphi method to develop a practical algorithm based on the ICS’s 2002 standardization of terminology in nocturia,<sup>1</sup> with a focus on what steps need to be taken before prescribing desmopressin.

## 2 METHODS

An initial consultation between 12 urologists was held during the ICS 2017 meeting in Florence, with participants representing the ICS, ICI-RS, European Association of Urology (EAU), and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU). Following the meeting, a nonsystematic keyword-based literature search was performed using Google (search on “guidelines 2010-2017” + symptom/sign/disease terms [edema, hypertension, heart failure, diet, menopause, male LUTS, OAB, prolapse, renal failure, diabetes insipidus, and diabetes mellitus]). All expert panel members were also invited to add any additional important guidelines from the different medical disciplines

relevant to the diagnosis and treatment of nocturia and its underlying causes. Some of these guidelines specifically target nocturia, and others aspire to target the underlying cause.

In areas where there was an absence of evidence and consistency between guidelines, the Delphi method was used to obtain an expert consensus—see Figure 1 for details. After the ICS 2017 meeting, a survey to gain views regarding the format, content, and additional panel members needed for the consensus report was distributed among nine of the urologists who agreed to participate as authors of the report, using the [www.surveymonkey.com](http://www.surveymonkey.com) platform (round 1); 75% agreement was needed to reach a consensus. As part of this round, it was decided that a broader range of experts should be included in the panel for round 2 to provide a multidisciplinary perspective. The initial Delphi panel for round 2 comprised of 20 clinicians, but 1 invitee did not respond to any of the rounds, and so the consensus was reached based on the views of the remaining 19 who participated. These 19 included 11 urologists (9 from the original group), 1 gynecologist, 1 epidemiologist/physiotherapist, 1 sleep specialist, 1 nephrologist, 1 geriatrician, 1 general practitioner, 1 neurologist, and 1 pharmacist. The Delphi panel members were asked to indicate whether they agree or disagree with statements about the diagnosis and treatment of nocturia patients. Again, 75% of the panel had to agree to achieve a consensus. If there was a criticism of the statement/question, it was reformulated for an additional subround, of which there were 2 in round 2 (Figure 1). In round 3, a different set of statements were presented to the multidisciplinary Delphi panel, and the same level of agreement was needed (ie,  $\geq 75\%$ ) for a consensus, but panel members were also asked to rate appropriateness of the statement on a scale of 1 to 9 (1-3 inappropriate; 4-6 uncertain; 7-9 appropriate). From the panel responses, a median appropriateness score was derived. As in round 2, if there was a criticism of the statement/question proposed, it was reformulated for an additional subround.



**Figure 1**

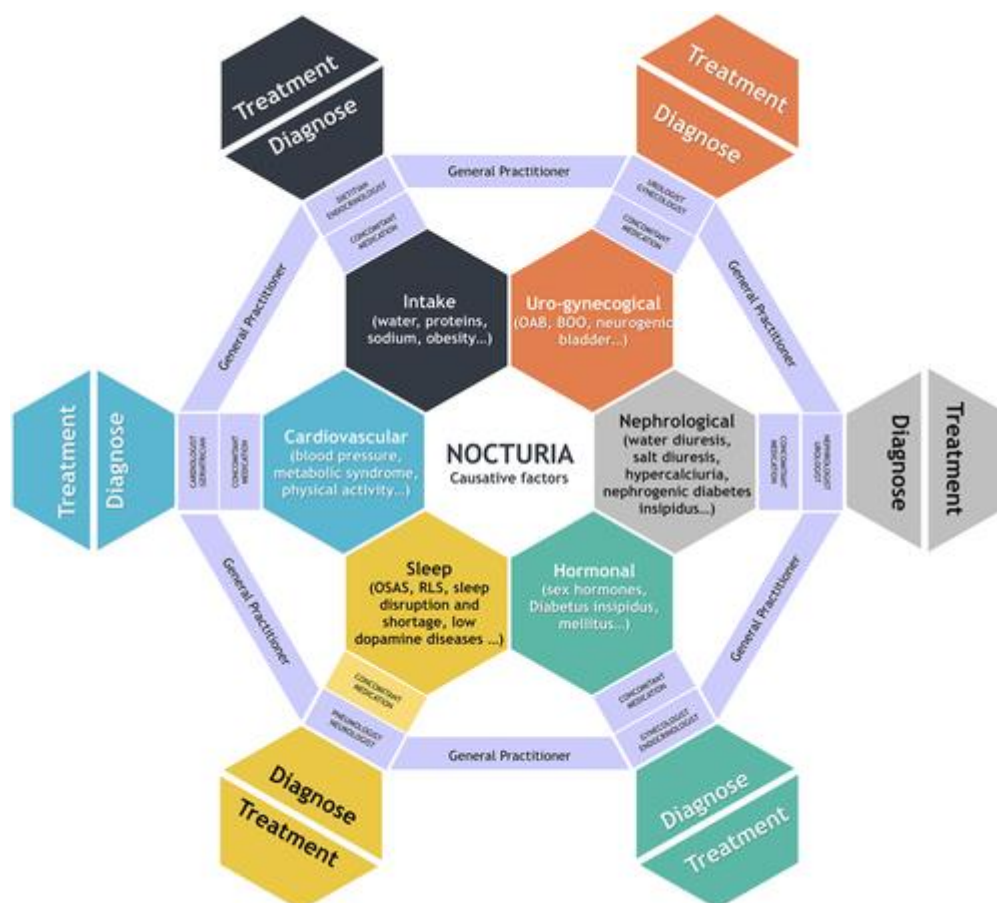
[Open in figure viewer](#)[PowerPoint](#)

Summary of the Delphi process [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

This consensus report on the diagnosis and treatment of nocturia is therefore based on real-life clinical practice, guideline/literature reviews, and where needed, an expert consensus obtained using the Delphi method.

## 3 RESULTS

The real-life diagnostic and therapeutic pathways for nocturia patients, based on the underlying causes of nocturia,<sup>6</sup> are summarized in Figure 2. There was a consensus that we should treat bothersome nocturia but there was no consensus on whether this should be confined to two or more voids per night, or include any level of nocturia. There was a consensus that nonbothersome nocturia, or convenient voids, should not be treated with desmopressin.



**Figure 2**

[Open in figure viewerPowerPoint](#)

Summary of the nocturia patient diagnosis and treatment pathways. Note that obesity can be indicative of excess caloric intake but is also associated with metabolic syndrome and is therefore also relevant to the cardiovascular pathway. Clinical specialties that deal with specific conditions may vary by country—for example, OSAS patients may be treated by a variety of specialists (including sleep, ear nose, and throat). BOO, bladder outlet obstruction; OAB, overactive bladder; OSAS, obstructive sleep apnea syndrome; RLS, restless legs syndrome [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

### 3.1 Diagnostic packages

The diagnostic packages in each subdiscipline dealing with nocturia patients are summarized below with reference to guidelines, prescribing information and the Delphi consensus—see Table 1 for an overview. History-taking, physical examination, and clinical assessment including disease-specific questionnaires (DSQ) are recommended diagnostic tools. The EAU 2018 guidelines suggest the severity and bother of individual LUTS (nocturia) should be identified with a symptom score, supplemented by directed questioning if needed. Examples of nocturia-specific questionnaires are the international consultation on incontinence questionnaire—nocturia; nocturia quality of life questionnaire, and the nocturia impact diary. In line with the diagnostic considerations from each of the relevant therapeutic areas, a

questionnaire has recently been developed to help to unify approaches to nocturia diagnosis.<sup>11</sup> The TANGO questionnaire is a short patient-administered screening metric designed to help the clinician assess nocturia and diagnose these different contributory mechanisms. Although some further validation is needed, the tool is available for clinical use in English and Dutch, and validation in French and Spanish is ongoing.

**Table 1.** Summary of diagnostic and therapeutic packages

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
Lower urinary tract		Nocturia within other guidelines (OAB, LUTS)	Nocturia, nocturia due to nocturnal polyuria		Bladder training (level 2 evidence)	OAB/BOO medication
	History and physical examination, DSQ	+	–	Consensus	Pelvic floor training (level 2 evidence)	dDAVP



	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
	Pelvic—digital rectal examination	+	—	If judged necessary		Consider combination therapy for refractory nocturia (Delphi consensus)
	PSA	+	—	If judged necessary		Botulinum toxin, sacral neuromodulation
	PVR	+ (weak)	—	Consensus		Prostatic and urethral surgery, prolapse correction
Kidney		Nocturia within other	Nocturia, nocturia due to		Salt, protein	No dDAVP if eGFR <50

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
		urological guidelines	nocturnal polyuria		and calorie restriction	(Delphi consensus)
	History and physical examination, DSQ	+	–			Consider dDAVP in low/moderate renal failure
	Need/use for/off questionnaire for screening NP	–	–	No consensus		Antihypertensive medication
	Bladder diary	+ 3 d	+	1. Consensus on the use of a diary, no consensus on duration (50/50) 2.		Dialysis

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
				<p>No consensus on the definition, NPI33 is widely used and practical but too sensitive. Use the right definition for the right population</p>		
	Baseline GFR estimation	+	+	<ul style="list-style-type: none"> <li>1.No consensus, as by PI</li> <li>2.Consensus no desmopressin below</li> </ul>		Kidney transplantation

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
				50 mL/kg/min		
	Baseline serum sodium	+	+	<ul style="list-style-type: none"><li>1.Age cutoff as by PI, consensus, but not stringent</li><li>2.Consensus s &lt;130 mmol/L is contraindication for desmopressin; majority (66%) prefers &gt;135</li><li>3.Timing and having an empty stomach or</li></ul>		Nephrectomy

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
				not are of no importance to the timing of test, consensus		
Hormones		Nocturia not mentioned	–		Sleep hygiene	Menopause-related nocturia should be treated with lifestyle interventions and HRT (Delphi consensus)
	History and physical examination, DSQ	+	–		Limit drinking	dDAVP for patients with blunted AVP secretion at night

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
Sleep	Serum LH, FSH, testosterone, estrogen	+	–		Bladder/pelvic floor training	
		Nocturia not mentioned	–		Sleep hygiene	CPAP in patients with OSAS (level 1a evidence)
	History and physical examination, DSQ	+	–		Weight loss	Sleep clinic/dDAVP in patients with insomnia, nocturia, and NP (consensus)
	Polysomnography	+	–	RLS: no consensus to refer/diagnose	Physical activity	Pramipexol, sleep aids
Cardiovascular and edema		Nocturia not mentioned	–		Physical activity,	Antihypertensive medication, timed diuretics

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
Intake					weight loss	
	History and physical examination and assess leg edema, DSQ	+	–		Salt restriction	dDAVP with caution only in those with Class I mild congestive heart failure and no severe leg edema
	BNP	+ (excludes heart failure if suspected)	–		Postural drainage stockings	Varicose vein surgery
	Nocturia not mentioned		+		Fluid restriction	Consider dDAVP
	History and physical examination,	+	+ (limited to fluid intake)	Consensus useful (fluid, food,	Salt, protein, and calorie restriction	Bariatric surgery

	Diagnostic				Therapeutic	
	Diagnostic test	Guidelines (see the Supporting Information Materials for refs.)	Prescribing information for dDAVP	Delphi panel	Lifestyle	Pharmacological
	DSQ, Intake diary			and calories)	– balanced diet	

- Abbreviations: AVP, arginine vasopressin; BNP, brain natriuretic peptide; BOO, bladder outlet obstruction; CPAP, continuous positive airway pressure; dDAVP, desmopressin; DSQ, disease-specific questionnaire; FSH, follicle stimulating hormone; GFR, glomerular filtration rate; HRT, hormone replacement therapy; LH, luteinising hormone; LUTS, lower urinary tract symptoms; NP, nocturnal polyuria; NPI33, nocturnal polyuria index >33%; OAB, overactive bladder syndrome; OSAS, obstructive sleep apnea syndrome; PI, prescribing information; PSA, prostate-specific antigen; PVR, post-void residual urine; RLS, restless legs syndrome.

### 3.1.1 The lower urinary tract package

History-taking with or without the use of validated questionnaires is structured based on symptoms of the filling phase and the emptying phase of the bladder.<sup>12, 4</sup> Physical examination focusses mainly on assessment of the prostate, vaginal examination for pelvic organ prolapse, and any urethral pathology, according to the relevant guidelines.

The 2018 EAU male LUTS guidelines<sup>4</sup> recommend to add urine analysis, serum prostate-specific antigen (PSA) test (if a diagnosis of prostate cancer will change the management), and to measure postvoid residual urine volumes.

Three-day bladder diaries, including sleep and wake up time, as well as the next morning's first void, have been recommended as giving the optimal balance between compliance and reliability.<sup>13</sup> The Delphi panel agreed (15/19) that it is necessary to demonstrate the presence



of NP using a bladder diary before prescribing desmopressin. There was no consensus on the duration of bladder diary required, including on whether patients with cognitive impairment or impaired executive function warrant the use of a shorter duration of bladder diary.

Approximately half of the panel (9/17) believe that all patients need to complete a 3-day diary; while the remainder (8/17) believe that the diary period can be shortened if the patient had his/her symptoms during the observation day. In the latter case, it would be necessary to include a question in the bladder diary regarding whether this was a typical night for LUTS, or if it was better or worse than usual, for example, to give an indication of whether the case night was indicative of the patient's condition. Even if there was an accurate questionnaire (>95% accuracy) that could predict NP, 13/18 (no consensus, 72%) would still ask patients to complete a bladder diary. This perseverance with the use of a bladder diary may reflect an underlying lack of conviction amongst the panel that such a questionnaire could feasibly be developed.

The maximum voided volume, void frequency, and the ratio of nocturnal to 24-hour urine production are the most used diary parameters to study and assess nocturia.<sup>14</sup> A maximum voided volume of 350 mL is generally considered as reduced without real evidence to support this criterion. When the nocturnal urine production exceeds the maximum voided volume, then nocturia is predictable, with some safety margin (nocturia index of >1.3 is generally accepted as a reliable cut-off).<sup>15</sup> The frequent causes of reduced voided volumes include an OAB and residual urine (secondary to obstruction or detrusor underactivity). A residual urine measurement is, therefore, part of the initial assessment of nocturia.<sup>4</sup> When reduced voided volumes are seen, imaging, urodynamics, and occasionally cystoscopy are performed, as appropriate.

Excessive nocturnal or 24-hour urine output is diagnosed using a bladder diary. According to the ICS definition, NP is diagnosed if more than one-third (>33%) of the 24-hour urine volume is produced during the night in patients over 65 years, and after excluding patients with 24-hour polyuria (>40 mL/kg/d). In the United States, the FDA's regulatory decision-making regarding desmopressin use has been based on these definitions. In younger people (21-35 years) the cut-off for NP is >20% of 24-hour urine.<sup>1</sup> No definition of NP between these age categories has been established. The "one-third" definition in older people is the most widely used definition and has a high sensitivity but low specificity. Other definitions are available,<sup>16</sup> but the most appropriate definition of NP is still the subject of much discussion.<sup>17, 18</sup> However, the definition of NP is not the scope of this document.

The Delphi panel considered that, in women, a pelvic examination is necessary before starting desmopressin either in all cases (7/19) or in those women with daytime symptoms (8/19)—an overall consensus of 15/19 in favor of pelvic examination.

There was a consensus from the panel that a PSA check need not be standard in all older men before starting desmopressin (0/18); 7/18 answered that there is no need to check PSA and 11/18 agreed that PSA measurement is only appropriate when considered necessary for other reasons. LUTS have no relation to PSA except in advanced prostate cancer (owing to the associated bladder outlet obstruction), and NP specifically is not associated with prostate cancer.

There was a consensus that older men with nocturia should complete a DSQ (13/17, median 7.4), post-void residual (14/17, median 7.4), bladder diary is mandatory (14/17, median 8.7), and there was no consensus on the need for a digital rectal examination (10/17, median 7).

### **3.1.2 Nephrological causes of nocturia and their diagnosis**

Renal causes of polyuria include renal diseases such as nephrogenic diabetes insipidus and loss of different circadian rhythms of the kidney, for example through aging of the kidney.[19](#), [20](#) Nephrogenic diabetes insipidus can also be caused by some medications, including lithium. Renal failure can also lead to leg edema with NP as a consequence.

When (nocturnal) polyuria is found, it is possible to diagnose the cause of the excess in urine output using renal function profiles.[19](#) These renal function profiles help in distinguishing whether the excess in urine production is due to an increase in free water clearance (vasopressin-related), osmotic diuresis (mainly salt, but can be urea [protein], glucose [diabetes], calcium [hypercalciuria], or lithium), or a combination. However, renal function profiles are only advised after the failure of desmopressin therapy, and for research purposes. In clinical practice, elevated free water clearance is the most frequent cause of NP throughout the lifespan and increases with age. The second most frequent etiology is an increased sodium clearance (eg, due to excess intake, leg edema, heart failure, hypertension, obstructive sleep apnea syndrome [OSAS], and medication), and this also increases with age. In summary, at first assessment, phenotyping (Figures [2](#) and [3](#)) based on history taking, concomitant medication and a general physical examination help the clinician to implement lifestyle interventions and therapies such as desmopressin (assuming minimum glomerular filtration rate [GFR] of 50 mL/kg/min).



**Figure 3**  
[Open in figure viewerPowerPoint](#)

Phenotyping nocturia for uncontrolled causalities when prescribing desmopressin, based on guidelines, prescribing information or Delphi panel. \*Based on evidence and guidelines to use CPAP for sleep apnea and the high levels of ANP and nocturnal salt loss. Conc, concentration; CV, cardiovascular; DI diabetes insipidus; DM, diabetes mellitus; Est, estrogen; E, efficacy; LUT, lower urinary tract; OSAS, obstructive sleep apnea syndrome; RLS, restless legs; S, safety; T, testosterone [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

### 3.1.3 Hormones and nocturia

Vasopressin is the main water-regulating hormone in our body. Vasopressin deficiency and vasopressin resistance of nephrogenic (receptor) origin are the main mechanisms leading to a lack of antidiuretic response within the body. The result is 24-hour polyuria and polydipsia, known as diabetes insipidus, which is a rare condition diagnosed via a bladder diary and a low morning (fasting) serum and urine osmolality. An abnormal circadian rhythm of vasopressin is the main mechanism for NP.<sup>21, 22</sup> Asplund described a lack of circadian rhythm in patients with NP and nocturia in both men and women,<sup>23</sup> but plasma levels in adults without nocturia peak at around 8 pg/mL in men and 4 pg/mL in women—both with a circadian rhythm.<sup>24</sup> These levels fall and a gender difference becomes more obvious in adults, as described by Graugaard et al,<sup>24</sup> and levels are even lower in the elderly, as described by Asplund. There is further evidence of an effect of the menstrual cycle in women,<sup>25</sup> which may also increase female sensitivity to desmopressin. If doses are given in identical strengths in men and women (not measuring the dynamic endpoint of NP), we would expect more safety concerns in women, especially elderly women. Vasopressin itself is difficult to measure as a routine test; copeptin is a by-product of vasopressin and is being explored as a biomarker of vasopressin levels.

The sex hormones are also involved in regulation of diuresis.<sup>26</sup> Deficiency in sex hormones (estrogen, testosterone) is diagnosed based on history taking and physical examination and

can be confirmed with blood analysis. Some validated questionnaires are available for diagnosing menopause. Nocturia is not discussed in these guidelines.[27](#)

### **3.1.4 Sleep and the central nervous system (CNS) as a cause of nocturia**

Sleep pathology, insomnia, and sleep disruption are well-known causes of NP and nocturia,[28](#), [29](#) and as such, they need to be diagnosed, especially as they are associated with morbidity and mortality.[30-32](#) In epidemiological studies, nocturia is associated with restless legs syndrome.[33](#) History taking and physical examination can be complemented with questionnaires including the Pittsburgh Sleep Quality Index,[34](#) which screens for both nocturnal and diurnal symptoms related to sleep disorders. The Berlin questionnaire[35](#) and the STOP questionnaire[36](#) are screening tools for OSAS. Polysomnography is performed when a diagnosis of sleep disorders is suspected.

Parkinson's disease and restless legs syndrome are conditions characterized by a dopamine deficiency.[37](#), [38](#) Sleep disruption and deprivation are associated with low dopamine levels in the central nervous system.[39](#) Both Parkinson's disease and restless legs syndrome are associated with NP and a reduced bladder capacity due to OAB and sphincter dysfunction.[40-42](#) However, a recent study suggested that the prevalence of NP in Parkinson's disease is no higher when compared with a control population, indicating some uncertainty in this regard.[43](#) The diagnosis of a brain- or sleep-related cause of nocturia is made clinically, and when suspected, patients need to be referred to neurologists or sleep specialists.

Evidence-based medicine[6](#) supports the need to refer and diagnose nocturia patients with suspected obstructive sleep apnea. Among the Delphi panel, there was no consensus whether suspected restless legs syndrome required a referral (9/17 [6 would treat NP simultaneously with referral]) or simply initiation of treatment for NP (8/17).

### **3.1.5 Cardiovascular causes of nocturia**

Hypertension is associated with nocturia and NP.[22](#) Nondipping hypertensive patients are a subgroup who do not exhibit a nocturnal reduction in blood pressure. There is an association between nondipping hypertension and nocturia,[44](#) and a specific association has been reported between NP and nondipping hypertension.[45](#) Children with enuresis have also been found to have higher nocturnal blood pressure than controls.[46](#) Nondipping hypertension is associated with increased morbidity.[47](#) In addition, postural hypotension with low blood pressures when standing results in higher blood pressures when supine. Diagnosis is simply made by measuring the blood pressure as part of the general clinical examination. Available guidelines in this area do not discuss nocturia.[48-53](#)

The metabolic syndrome is strongly associated with nocturia and many conditions predisposing to NP,[54](#), [55](#) and it is an important burden for healthcare systems worldwide. The condition needs to be diagnosed when clinically suspected in patients with nocturia. Again, available guidelines in this area do not mention nocturia.[57](#), [56](#)

Heart failure often coincides with renal failure (30%-40%) and correlates with increased mortality. This cardio-renal syndrome presents as elevated brain natriuretic peptide (BNP) with hypovolemia (normal serum sodium) or as overfilling (hyponatremia). Both conditions coincide with an elevated creatinine, a bad estimator of GFR in these patients, and demand referral before initiation of desmopressin or timed diuretic therapy.[58](#)

Right-sided heart failure, in particular, is characterized by fluid retention and swelling of the abdomen, legs, and feet (<https://www.mayoclinic.org/diseases-conditions/heart-failure/symptoms-causes/syc-20373142>). Edema, and especially leg edema, causes NP and nocturia through resorption of fluid when supine,[59](#), [60](#) resulting in an immediate excess in urine output and a delayed increase in ANP-related salt diuresis. Leg edema is seen with liver, heart or kidney disease or following varices of the legs, lack of physical activity or muscle paralysis. Concomitant medications that can cause edema are listed in the section below on concomitant medication. Diagnosis of edema is based on expert opinion rather than empirical evidence, and the available guideline documents for edema do not mention nocturia.[48](#), [49](#)

As mentioned above, there was a consensus that older men with edema and nocturia should complete a DSQ (13/17), have a postvoid residual measurement (14/17), and a clinical evaluation of cardiovascular and leg edema (13/17); a bladder diary is mandatory (17/17). There was no consensus on a digital rectal examination (10/17). There was a consensus that older people with nocturia should have their blood pressure measured (13/17, median appropriateness 8). Older people with leg edema and nocturia were considered likely candidates for cardiovascular aetiological factors (13/17, median appropriateness 7), and it was agreed that clinical examination should focus on this pathophysiology (13/17, median 7).

### **3.1.6 Fluid and food intake as a cause of nocturia**

High intake of water, salt, or protein results in an increased excretion by the kidney and can result in NP and nocturia. An excess intake of osmoles leads to thirst, and increased fluid intake—a second reason for NP. An excess intake of calories results in obesity which may, even without the presence of the metabolic syndrome, result in NP due to the higher intra-abdominal pressure, mainly when supine, as a result of obstruction of the respiratory tract.[61](#) History taking, physical examination, recording of fluid and food intake on a bladder

diary, and hypothetically renal function profiles can diagnose the excess of intake of sodium (salt) and ureum (protein).[62](#), [63](#)

Dietary guidelines discuss the treatment of obesity[56](#), [64](#) but nocturia-related recommendations are not available. The consensus panel agreed that it is appropriate (13/17, median appropriateness 7) to investigate caloric intake and physical activity through history taking and/or diaries.

### **3.1.7 Concomitant medication leading to nocturia**

Concomitant medication is often difficult to interrupt or change but might have an important impact on nocturia through increasing or decreasing diuresis, changing bladder function, or through interfering with sleep. Other factors that will influence the impact of concomitant medication are the timing of administration, mode of administration, formulation (long- vs short-acting), and so on. Most of these factors have not been well studied.[3](#), [14](#)

For many medications, the net result on diuresis (water and osmotic diuresis) is unknown and insufficiently studied, and many medications have contradictory effects on water and osmotic diuresis. Even desmopressin, known to solely impact on free water excretion, can cause water retention resulting in renin-angiotensin-aldosterone system suppression, ANP, release and osmotic diuresis.

Another example of the contradictory effects of concomitant medication is calcium channel blockers—these increase salt excretion[65](#) to lower blood pressure, but side effects include leg edema, which can potentially worsen nocturia when the edema fluid is resorbed during the night.

Medications that typically increase diuresis are diuretics, all antihypertensive medication, progesterone, melatonin, lithium, and SGLT-2-inhibitors (antidiabetic patients).[6](#) Other medications decrease diuresis, such as the older antidiabetic patients, antidepressants, antiepileptics, estrogens, testosterone, corticoids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Medications that typically cause leg edema are antidepressants (monoamine oxidase inhibitors, trazodone), antihypertensives (beta-blockers, clonidine, hydralazine, methyldopa, minoxidil and so on), antivirals (acyclovir), hormones (sex hormones), NSAIDs (celecoxib, ibuprofen), and some chemotherapeutics and cytokines.[6](#)

There is a consensus that the following conditions are a contraindication for desmopressin: congestive heart failure (16/19), polydipsia (15/19), and concomitant medication with a high risk of hyponatremia (16/19).[66](#) There was no consensus for peripheral edema (12/19),

uncontrolled hypertension (13/19), uncontrolled diabetes (11/19), and oral steroids (6/19). For nasal/inhalation steroids there was a reversed consensus (0/19).

Diagnostic packages:

- Consensus on history taking or questionnaires for all causalities.
- Pelvic (women) or rectal (men) examination when judged necessary.
- Blood pressure and edema check is necessary.
- Consensus for bladder diary, but not for its duration (3 days suggested).
- Consensus for diaries on sleep, intake (fluid and food), and physical activity.
- Consensus for postvoid residual measurements.
- PSA, serum sodium check (SSC), renal/heart function, and endocrine screening when judged necessary.
- Timing or empty stomach when SSC performed is not important.

## 3.2 Therapeutic packages

Lifestyle interventions targeted towards the aetiology of nocturia may be useful in some patients (Figure [4](#)).





**Figure 4**  
[Open in figure viewerPowerPoint](#)

Lifestyle interventions in nocturia according to pathophysiology. DM, diabetes mellitus  
 [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

### 3.2.1 Lower urinary tract therapy

There is level two evidence that treating dysfunctions of the bladder and the prostate (eg, OAB and BPO) with lifestyle interventions such as bladder training and pelvic floor training, or evening exercise (eg, walking the dog), as well as medication or surgery, improve nocturia.<sup>6</sup>

There was a consensus from the panel that combination therapy should be considered for nocturia that is refractory to initial treatment (18/19).

### 3.2.2 Nephrological causes of nocturia and their therapy

Lifestyle interventions aim to prevent rather than treat renal disorders, for example by avoiding obesity, hypertension, and diabetes. Salt, protein, and caloric restriction are advised in patients with renal failure but there is no evidence of its effect on nocturia. Desmopressin can have some effect in partial nephrogenic diabetes insipidus but is not the primary choice in patients with severe renal failure as the risk of hyponatremia is much higher (Table [3](#)). For



those undergoing an investigation of renal function, there was a consensus that desmopressin should not be prescribed if eGFR is <50, and that higher limits are dependent on local prescribing information. In patients with low to moderate renal failure, as is seen in most of the older population, a loss of circadian rhythms in diuresis is found and these patients are potentially good candidates for desmopressin therapy.

### **3.2.3 Hormones and nocturia therapy**

In the 2002 standardization document,<sup>1</sup> low estrogen and menopause are recognized as a cause of nocturia, and androgen deprivation is also associated with LUTS and nocturia. There is no evidence-based medicine to demonstrate that hormonal substitution in postmenopausal women is an effective treatment of nocturia (ICI-RS 2017).<sup>26</sup> The 2015 NICE guidelines (<https://www.nice.org.uk/guidance/ng23>) state that there is a good evidence that hormonal substitution is helpful for vasomotor symptoms (hot flushes) and for vaginal atrophy and its consequences, but do not mention nocturia.

There was a consensus that menopause-related nocturia and hot flushes should be treated with lifestyle interventions and hormone replacement therapy (17/18). These approaches were not considered useful when menopause is asymptomatic, except for nocturia (5/18). Desmopressin should not be given during the first treatment consultation in the presence of menopausal symptoms (1/18 if menopausal symptoms), but when there is nocturia without menopausal symptoms, there was nearly a consensus that desmopressin can be given (13/18 [74%]).

Patients with NP due to a blunted increase in AVP secretion at night, leading to an increase in free water clearance, are good candidates for desmopressin therapy.<sup>67</sup> Patients with 24-hour polyuria due to central diabetes insipidus (in which production of AVP is compromised) are also effectively treated with desmopressin,<sup>68</sup> which is in these cases a type of hormone replacement therapy.

### **3.2.4 Sleep and the CNS in nocturia therapy**

There is level 1a evidence for the use of CPAP in patients with OSAS. There is only low level 2 or lower level evidence that sleep aids, treatment of low dopamine and treatment of restless legs syndrome have an impact on nocturia (ICI-RS 2015).<sup>42</sup>

There was a lack of consensus from the panel regarding the treatment of patients with insomnia, nocturia, NP, and a diagnosis of RLS. There was no consensus (10/17) whether patients with insomnia and NP should be treated for insomnia and with desmopressin at the same time (median appropriateness was 7). There was no consensus on treating RLS, insomnia, insomnia with RLS, or NP with RLS and insomnia in any combination.

In patients with insomnia, nocturia, and NP without a diagnosis of RLS, there was a consensus to treat NP (14/17) but this was split across treatment of NP per se (8/17), referral to a sleep clinic (3/17), or both (6/17). Reasons for this lack of agreement across the panel on the appropriate steps may relate to a lack of evidence on which to base treatment of insomnia with nocturia/NP, or perhaps to the range of specialisms in the group with inconsistent views on the role of other disciplines, e.g., for example, sleep medicine.

### **3.2.5 Cardiovascular causes of nocturia and their therapy**

There is ample evidence that treating heart conditions, increasing physical activity, salt restriction, losing weight, and preventing edema treats nocturia.[6](#)

Desmopressin for nocturia is contraindicated in patients with mild (class II) to severe (class IV) congestive heart failure (New York Heart Association Class II to IV) or uncontrolled hypertension, and should be used with caution (eg, monitoring of volume status) in patients with New York Heart Association Class I mild congestive heart failure because of the risk of fluid overload and electrolyte abnormalities. Patients with heart failure may also be at increased risk for low sodium concentrations.[69](#)

In people with moderate cardiac failure, there was a consensus that this condition should be treated before any attempt to address nocturia specifically (16/17, median 9). Use of desmopressin in such cases is completely inappropriate (16/17, median 2). There was no consensus concerning the use of daytime furosemide (4/17, median appropriateness 5).

In older people with NP, nocturia, and hypertension, there was no consensus as to whether hypertension should be treated first (11/18, median appropriateness 7). Treatment of NP first was considered inappropriate by 8/17 (median 4). The treatment of hypertension and NP simultaneously also had no consensus (5/17 inappropriate, 6/17 uncertain, and 6/17 appropriate; median appropriateness 5). The Delphi panel did not consider it useful to change antihypertensive drugs or their timing (other than diuretics) (8/17, median 6) to address nocturia.

In patients with varicose veins but no cardiac failure, there was no consensus on treating veins first (9/18, median 6) nor on using desmopressin first (10/17 inappropriate, 3/17 uncertain, and 4/17 appropriate; median 4).

### **3.2.6 Intake as a target of nocturia therapy**

Limiting excess fluid intake and changing the type of fluid is advised in most LUTS guidelines.[70](#) Less is known about the effect of diet and weight loss.[6](#) Weight loss will decrease hyperfiltration and diuresis. Low protein intake will decrease salt and ureum output and osmotic diuresis. Salt restriction might decrease osmotic diuresis. Low carbohydrate

intake will not change diuresis directly. Low fat intake will not directly affect diuresis. During most diets, an increase in water intake is advised, increasing water diuresis. In conclusion, from a theoretical, nonevidence-based viewpoint, a protein-rich and fat/carbohydrate-restricted diet might increase urine output as well as reduce it in the longer-term via weight loss. A well-balanced calorie-restricted diet seems the most logical approach to avoid high excretion of ureum and salt in patients with nocturia. In general, guidelines suggest caloric restriction and summarize that a high protein intake results in more efficient weight loss.[57](#), [56](#)

There was no consensus from the Delphi panel on appropriate therapeutic options for patients with high BMI and nocturia (including losing weight [no consensus 9/18, median appropriateness 6]; weight loss with desmopressin [5/18, median 5]; desmopressin alone [6/18, median 5]; and adapting diet when there is a high osmotic load [6/18, median 5]).

Therapeutic packages:

- There is only good evidence for desmopressin and for CPAP.
- For all other therapies, the evidence is moderate (furosemide, OAB-BPH medication) or weak for most causalities.
- The safe candidates for desmopressin can be phenotyped as no polydipsia, heart/kidney failure, severe leg edema, or OSAS.

### 3.3 Initiating desmopressin treatment

NP due to reduced nocturnal vasopressin is the primary target for desmopressin. Salt-related NP is associated with other causes such as sleep apnea (the primary target for CPAP), edema, obesity, hypertension, heart failure, and high salt intake. There is level 1a evidence that desmopressin and CPAP treat nocturia.[7](#), [4](#) A summary of the prescribing information for available desmopressin formulations for nocturia from the United States, Australia, and Europe is given in Table [2](#).

**Table 2.** Prescribing information for different desmopressin formulations indicated for nocturia, which is likely to influence clinician judgments

	<b>Desmopressin 0.2 mg, tablets</b>	<b>Nasal spray 0.83- 1.66 µg/0.1 mL (Noctiva)</b>	<b>Sublingual wafers 25-50 µg, (Nocdurna)</b>
Age for baseline sodium checks and follow up	65	65	65
Fluid restriction	Restrict	Moderation advised (do not drink large amounts close to bedtime)	Restrict 1 h before to 8 h after administration
GFR (lower limit for prescribing)	50 or 60 <sup>a</sup>	50	50-60 <sup>a</sup>
Sodium checks after baseline (≥65 y)	3 d + after uptitration	Within 7 d + after uptitration	4-8 d + 1 mo or 4-8 d, 1 mo, every 3 to 6 months, depending on clinical need
Cardiovascular contraindication	Cardiac insufficiency or conditions requiring diuretics	NYHA class II or higher CHF  Diuretic use	Heart failure, edema
Frail elderly	Not mentioned	Not mentioned	Contraindicated

- CHF, congestive heart failure; GFR, glomerular filtration rate; NYHA, New York Heart Association
- <sup>a</sup> Moderate to severe renal failure or <50-60 mL/min depending on the formula used and cut-off used.

The panel agreed that bothersome nocturia should be treated (17/19); however, there was no consensus regarding what level of severity warrants treatment ( $\geq 2$  voids/night [5/19], or any nocturia [12/19]). It was agreed that nonbothersome nocturia or convenience voids (ie, secondary to waking for a different reason) should not be treated with desmopressin (1 and 0/19).

There was no consensus among the Delphi panel as to an appropriate age limit above which serum sodium should be checked before desmopressin treatment. This was also true for renal function (eGFR). This lack of consensus is likely affected by differences in prescribing information and recommendations between countries. However, there was a consensus that any age limit should not be treated too stringently, and patients who are near the limit may also be checked before treatment (17/19).

The Delphi consensus was that patients with a baseline serum sodium of  $\leq 130$  mmol/L should not be prescribed desmopressin (18/19), with the panel split between a cut-off of  $>130$  mmol/L (6/19) and  $>135$  mmol/L (12/19) for treatment. Again, the panel's views on this issue might be influenced by regional regulatory rules and prescribing information.

Dilutional hyponatremia takes several days of positive water balance to build up. To decrease by 5 mmol/L a positive water balance of 2 L is needed. There was a consensus (15/17) that SSCs can be performed at any time of day and are not affected by whether or not the stomach is empty (although note that polydipsia is a contraindication of the drug). There is sufficient literature to support that a sodium check can be done at any time of the day.[71](#)

The following conditions are agreed to be contraindications for desmopressin use: congestive heart failure (16/19), polydipsia (15/19), and concomitant medication with a high risk of hyponatremia (16/19). Concomitant medication with low risk for hyponatremia (5/19), peripheral edema (12/19), uncontrolled hypertension (13/19) or diabetes (11/19), oral steroids (6/19), and nasal steroids (0/16) did not reach consensus.

The panel agreed that women are more prone to hyponatremia and that this should have implications for desmopressin therapy and its follow-up (16/19). There is a consensus that some form of fluid restriction is needed by patients prescribed desmopressin (18/19)—either following thirst (14/19) or strict fluid restriction (4/19).

With earlier formulations of desmopressin (0.2 mg tablets), hyponatremia was seen mainly in older populations, leading to a restriction in use to those below 65 years of age. Lowering the dose to provide an antidiuretic effect of 6 to 8 hours was the logical way to treat the older (especially female) population. Low dose therapy is not a well-defined term but is today the best way to describe the newer formulations in the market, which have both been tested in an

older population. Low dose therapy is advisable in older (but not frail) patients and serum sodium monitoring is needed; such monitoring can be individualized depending on patient-specific factors (eg, age, concomitant medication) and comorbidities (16/19). Frail older patients with bothersome nocturia and comorbidities or other risk factors should first be treated for other issues and comorbidities and then, if still required, desmopressin should be initiated with careful monitoring (15/18).

Young healthy patients can be treated with any licensed desmopressin formulation (15/18).

Initiating desmopressin:

- Risk management consensus on classification into three clinical pictures: (1) standard vigilance to symptoms of hyponatremia, (2) SSC, and (3) contraindications.
- Decision-based on age, renal function, heart failure, frailness, edema, baseline serum sodium, drinking habits, and medication.
- Low-dose formulations preferred in patients needing SSC.

### 3.4 Follow-up of desmopressin therapy

Critical to the appropriate use of desmopressin and its analogs is an established schema for monitoring of sodium homeostasis in the acute and chronic phase of therapy. Contingent on stable dosing and otherwise unchanging comorbidities is the realization that shifts in fluid ingestion may potentiate the risk of hyponatremia in an otherwise stable patient. Therefore, an informed and the engaged patient is critical to desmopressin safety. In addition, acute alterations in concomitant comorbidities should be assessed for their potential to impact sodium levels.

There are various approaches to sodium monitoring in the literature. Before starting therapy, baseline sodium levels must be obtained in patients at risk for hyponatremia. Bioavailability and formulation delivery appear to have an impact on desmopressin half-life and the area under the curve (indicative of drug exposure), both of which impact the risk of hyponatremia.<sup>17</sup> There is some evidence from analysis of a merged database<sup>17</sup> that a sodium monitoring plan should begin with a baseline sodium  $\geq 135$  mmol/L with additional SSC at week 1 and month 1 after initiation of desmopressin in patients who are at increased risk (eg, due to older age, or concomitant medications). This conclusion is based on the fact that most clinically significant cases of hyponatremia were seen within 2 to 3 weeks of treatment initiation. A noteworthy observation is that time to return to normal after cessation of treatment was a median of 17 days (range 8-28).

As the optimal monitoring schedule is often debated, the Delphi panel was consulted. When baseline serum sodium levels were judged necessary, there was a consensus that serum sodium should be checked on a fixed schedule, beginning within 7 days of desmopressin initiation, but with no consensus regarding exactly when in the first week this should occur (Day 3 [7/19] or Day 5-7 [9/19]). Weekly blood samples were not deemed necessary (1/18); 4/18 preferred 2-weekly and 13/18 (or 72%; no consensus) agreed that samples should be taken at the discretion of the physician. There was a consensus to perform an SSC as judged by the clinician at 1 month (17/18). Beyond 1 year, there is no consensus on follow up required—10/18 agree that monitoring should be performed when the patient's medical condition (eg, hospitalization, fever) or concomitant medication changes; 8/18 agreed with annual checks.

In young healthy patients, there was no consensus on SSC needed—the majority believed no checks were necessary (11/18), assuming no underlying medical conditions.

There was a consensus that some form of fluid restriction should be advised for all patients (only 1/18 found it unnecessary)—the consensus was split between advising patients to follow their own thirst (14/18) and strict fluid restriction (4/18).

If the response to desmopressin is insufficient at a low dose, there was a consensus that dose should be up-titrated (18/19), depending upon the frailty of the patient (11/19). An SSC should be carried out before up-titration, depending on the patient (17/19). If the dose is up-titrated and further sodium checks are appropriate (15/19), these should be carried out within 7 days.

If hyponatremia is found after initiating desmopressin therapy, there is a consensus (15/19) that treatment should be discontinued when an SSC is below 130 regardless of the presence of symptoms. If sodium check is between 130 and 135 and the patient is asymptomatic, treatment need not be discontinued (only 1/19 would stop the therapy), but further checks (8/19) or drug-free intervals (3/19) or lowering the dose (7/19) should be performed. See Figure 5 for a summary.



**Figure 5**  
[Open in figure viewerPowerPoint](#)

Follow-up after desmopressin prescription when serum sodium checks wanted or needed. Symptoms of hyponatremia include: nausea and vomiting, headache, confusion, loss of energy, drowsiness, and fatigue, restlessness and irritability, muscle weakness, spasms or cramps, seizures, and coma. FU, follow up; SSC, serum sodium check [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

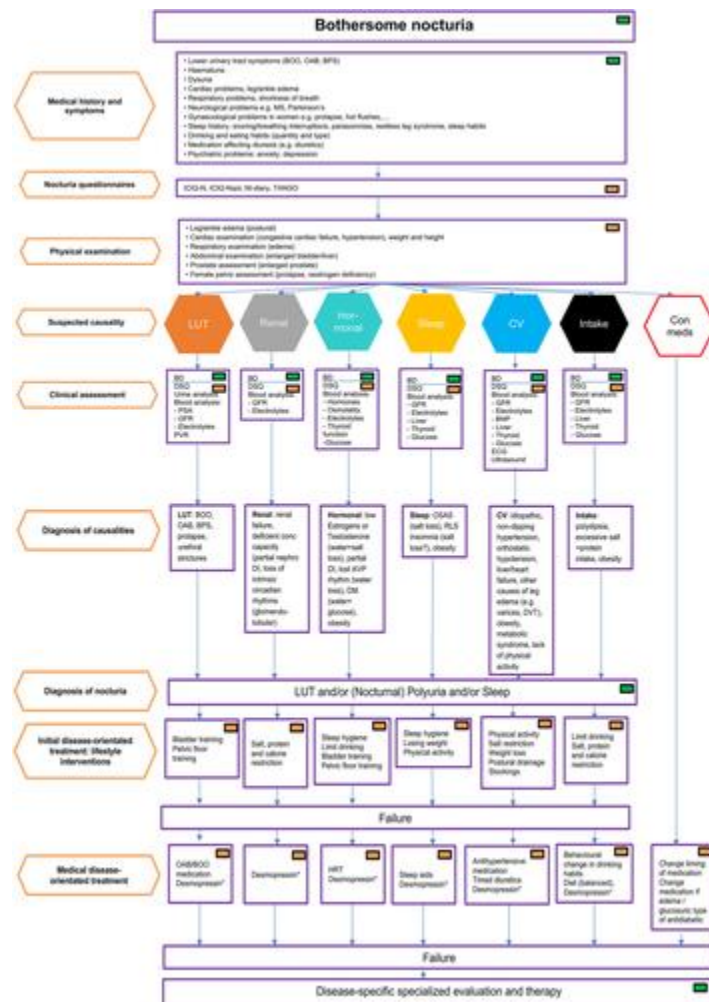
Follow-up of desmopressin therapy:

- If SSCs are necessary, follow-up on day 3 to 7 and 1 month.
- Further checks at clinician discretion.
- Stop therapy if serum sodium is  $<130$  mmol/L regardless of hyponatremia symptoms, and if serum sodium is 130 to 135 mmol/L with symptoms.

### 3.5 Patient-oriented nocturia care path




Based on existing guidelines, evidenced-based medicine, and the Delphi panel, we developed a patient-oriented multidisciplinary diagnostic and therapeutic algorithm for bothersome nocturia, aiming for a more holistic approach to nocturia from a multidisciplinary angle (Figure 6). The aim of this algorithm is to ease the work of clinicians and shorten the time to treatment.



**Figure 6**  
**[Open in figure viewerPowerPoint](#)**

A patient-oriented multidisciplinary diagnostic and therapeutic algorithm for nocturia. \*If desmopressin, consider Figure 3 and Table 3 before initiating, and consider Figure 5 for follow-up. BD, bladder diary; BNP, brain-derived natriuretic peptide; BOO, bladder outlet obstruction; BPS, bladder pain syndrome; Con Med, concomitant medication; CPAP, continuous positive airway pressure; CV, cardiovascular; DI, diabetes insipidus; DM, diabetes mellitus; DSQ, disease-specific questionnaires; DVT, deep venous thrombosis; ECG, electrocardiogram; GFR, glomerular filtration rate; HRT, hormone replacement therapy; LUT(S), lower urinary tract (symptoms); MS, multiple sclerosis; OAB, overactive bladder; OSAS, obstructive sleep apnoea syndrome; PSA, prostate-specific antigen; PSG, polysomnography; PVR, post void residual; RLS, restless legs syndrome. ■

consensus,  consensus “when judged necessary by the clinician,” “combinations possible”  
[Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

## 4 DISCUSSION

Diagnostic and treatment packages (Figure 2) are helpful in the visualization of the pathway of nocturia patients. We believe they could be a useful educational tool for training of healthcare professionals to improve patient care for nocturia, to limit the hurdles a patient has to get over to receive appropriate care and decrease the time to treatment.

The lifestyle interventions that are recommended in all LUTS guidelines are a good case in point. There is a growing interest globally in lifestyle interventions as a possible treatment for LUTS and, therefore, also for nocturia. The International Consultation on Incontinence summarized the need for research on conservative management of incontinence,<sup>72</sup> and the possible lifestyle interventions that can be relevant in nocturia are weight loss, diet change, fluid intake modification, and exercise. Of these, weight loss and fluid management have a fair amount of scientific data to support their impact. Weight loss (Level 1 evidence) is mentioned as a first-line treatment to reduce the prevalence of urinary incontinence with a Grade A recommendation. Restricted fluid intake, which could decrease the voiding frequency, urgency, and volume is mentioned with a Grade B recommendation. For nocturia specifically, no such high levels of evidence exist, with the exception of fluid restriction (Level 1b). In contrast, expert opinion supports weight loss, diet, foods, salt restriction, and protein restriction in the therapy of nocturia.<sup>6</sup> This shows an important scientific knowledge gap in our understanding of approaches to the reduction of LUTS and nocturia.

There are a number of strategies to manage the risk associated with desmopressin therapy (namely hyponatremia risk). In young healthy people with nocturia, it is advised that any desmopressin formulation can be used, and dose can be up- or down-titrated when needed. In older people, the factors summarized in Table 3 should be checked, and a low dose formulation should be used or the patient should be excluded from desmopressin therapy. It is safer to start with a lower dose and to lower the threshold to perform SSC in women compared with men as women have a higher sensitivity to desmopressin and are more prone to hyponatremia. This gender difference in antidiuretic response has been found in animal studies<sup>73</sup> and in clinical studies.<sup>74, 75</sup> In female rats, it was shown that this gender difference is explained by a significantly higher expression of the V2 receptor in females.<sup>73</sup> It was suggested that this was caused by escape from X-chromosome inactivation by the X-linked V2R gene, causing increased V2R dosage in females.<sup>76</sup>

**Table 3.** Consensus summary of risk management for hyponatremia when considering desmopressin administration

<b>Risk management</b>	<b>Standard vigilance to hyponatremia symptoms</b>	<b>Standard vigilance to hyponatremia symptoms + serum sodium check (SSC)</b>	<b>Contraindication</b>
	< 65 y	65 y or older	Frail older people
	Baseline sodium > 135	Baseline sodium 130-135	Baseline sodium below 130
	eGFR > 50-60	eGFR 50-60	eGFR <50
	No concomitant medication that can cause hyponatremia	Concomitant medication weakly or moderately related to hyponatremia	Concomitant medication strongly related to hyponatremia
	No leg edema	Low to moderate leg edema	Important leg oedema
	No heart failure	Heart failure (NYHA class I)	Heart failure (NYHA class II or higher)
	No diabetes mellitus or hypertension	Controlled diabetes mellitus or hypertension	Uncontrolled diabetes mellitus or hypertension
		Need for a higher dose, up-titration	Psychogenic polydipsia (>3 L/d)
		Higher risk in women	Higher risk in women

<b>Risk management</b>	<b>Standard vigilance to hyponatremia symptoms</b>	<b>Standard vigilance to hyponatremia symptoms + serum sodium check (SSC)</b>	<b>Contraindication</b>
Formulation	Any desmopressin formulation	Low dose desmopressin	Treat condition if possible and wait with desmopressin
SSC	No consensus on SSC	Consensus on SSC	—

High-risk medications for hyponatremia are thiazide diuretics, lithium, valproate, and carbamazepine<sup>66</sup> and use of these should be considered as a contraindication for desmopressin therapy. Low-to-moderate risk medications for hyponatremia are loop diuretics, antidepressants, ACE-inhibitors, and angiotensin-II-receptor blockers. These can be used concomitantly with desmopressin after consideration of the other factors from Table 3; concomitant use necessitates follow-up and sodium monitoring. Based on studies with loop diuretics,<sup>6</sup> it is wise not to start both medications at the same time, but to allow an interval of 2 to 3 weeks between their initiation to help the kidney in resetting its salt gradient before administering the second drug.

Since it is important to consider the frail elderly as distinct from other older persons for the purpose of desmopressin therapy, a definition of what is meant by frailty would be helpful. Perhaps the combination of a clinical frailty scale and a Timed Up and Go test (to assess a person's mobility using static and dynamic balance) would capture enough about frailty for most clinicians. The modified frailty index is an 11 item frailty index described for noncancer gynecological patients which captures enough information to detect adverse outcomes and this might be useful.<sup>77</sup> There is also the G8 survey, which captures "frailty."<sup>78</sup> Regarding comorbid conditions, a Charleston comorbidity index would be of use, although it is somewhat limited in older people by a lack of variability.

In the consideration of heart failure and its diagnosis in nocturia patients, heart failure should be suspected when there is a history of heart disease, when edema and/or weight gain with rapid onset is found and/or a patient complains of exertional dyspnea or orthopnea. A normal serum BNP concentration rules out uncontrolled heart failure. It is clear that when this condition is suspected, even in mild form, clinicians should be careful with prescribing desmopressin and it is better to refer the patient to a cardiologist and await instructions.

The monitoring of serum sodium in nocturia patients treated with desmopressin lacks sufficient evidence to produce good guidelines. As hyponatremia is rare in well-selected patients with the currently available low-dose formulations, producing strong evidence for a safety protocol will be difficult. It is likely that complex statistical studies on merged databases may be a promising strategy for the future and could help to produce a personalized medicine algorithm for serum sodium monitoring after desmopressin initiation. In the meantime, clinicians should err on the side of caution, even if it means more SSC.

From a clinical scientific perspective, when looking at Table [2](#), it would be interesting to demonstrate the actual plasma levels of desmopressin following the use of the three different formulations, as this explains better the rationale for the dose differentiation. We would suggest focussing on pharmacodynamic studies combined with pharmacokinetic studies to evaluate the strength and duration of the antidiuretic effect, and the effect on serum sodium levels. These studies would ideally be performed in nocturia patients during an overnight evaluation, as performed by Goessaert et al.[79](#)

It is clear from this Delphi panel experience that items which suffer from a lack of evidence in the literature are difficult to form a consensus on with a multidisciplinary panel. This demonstrates the need for more studies on some of the smallest steps in the care path of nocturia patients. However, the performance of studies that are crucial to our understanding, but do not attract funding from the pharmaceutical industry (eg, effects of lifestyle interventions), will be challenging, as will be the study of low-frequency events and patient risk factors. There is also a difficulty in reaching consensus in relation to diagnostic tests such as serum PSA or clinical prolapse evaluation as the guidelines in these areas originated from urological or gynecological organizations (and indirectly from studies on urological and gynecological patients), whereas the Delphi panel is multidisciplinary and clearly votes from this broader perspective. Our algorithm needs more research mainly in relation to the causalities of the cardiovascular system and intake-related aetiologies. Even in urogynecology, many questions remain unanswered such as the efficacy of medication in nocturia patients with a reduced bladder capacity. For sleep disorders, little research has been done on restless legs syndrome and insomnia as a cause of nocturia. Finally, there is a need to study nocturia based on this multicausal origin, as well as from a diagnostic and a therapeutic angle. Development of a standalone evidence-based nocturia guideline will probably originate from a multidisciplinary organization, and in the future, we envisage that the nocturia care path will move away from the disciplines of urology and gynecology towards less narrowly focused specialisms such as internal medicine, geriatrics, and general practice.

## 5 CONCLUSION

A summary of the nocturia patient pathway across different medical specialisms is useful in the visualization and phenotyping of patients for diagnosis and therapy. It also highlights that nocturia is in general not a urological symptom, but predominantly a symptom of a wide variety of causalities, many of which are easy to screen for with history taking, questionnaires, and physical examination. By providing some basic knowledge of desmopressin, its contraindications, safety concerns and follow-up here, we aim to ease its initiation for clinicians and to shorten the patient journey for nocturia.

## ACKNOWLEDGMENT

We would like to thank all the Delphi panel Members: Paul Abrams: Bristol Urological Institute, University of Bristol, Bristol, UK; Marco Blanker: University of Groningen, Department of General Practice, Groningen, The Netherlands; Donald Bliwise: Department of Neurology, Program in Sleep, Aging and Chronobiology, Emory University School of Medicine, Atlanta, Georgia; Ruud Bosch: Urology Department, UMC Utrecht, Utrecht, The Netherlands; Wendy Bower: Department of Medicine and Community Care, University of Melbourne, Melbourne, Australia; Chris Chapple: Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, University of Sheffield, Sheffield, UK; Roger Dmochowski: Urology Department, Vanderbilt University Medical Center, Nashville, Tennessee; Marcus Drake: Bristol Urological Institute, University of Bristol, Bristol, UK; Karel Everaert: Urology Department, Ghent University Hospital, Ghent, Belgium; Hashim Hashim: Bristol Urological Institute, University of Bristol, Bristol, UK; Francois Hervé: Urology Department, Ghent University Hospital, Ghent, Belgium; Kristian Juul: Ferring Pharmaceuticals A/S, Copenhagen, Denmark; Sherif Mourad: Urology Department, Ain Shams University, Cairo, Egypt; Jalesh Panicker: Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, UK; Dudley Robinson: Urogynaecology Department, Kings College Hospital, London, UK; Johan Vande Walle: Department of Paediatric Nephrology, Urology Center, Ghent University Hospital, Ghent, Belgium; Philip Van Kerrebroeck: Urology Department, Maastricht University Medical Center, Maastricht, The Netherlands; Adrian Wagg: Division of Geriatric Medicine, University of Alberta, Edmonton, Canada; Alan Wein: Urology Department, University of Philadelphia, Philadelphia, Pennsylvania; Jeff Weiss: Department of Urology, SUNY Downstate College of Medicine, New York City, New York.

We would also like to thank Caroline Loat, PhD for editorial assistance.

- 1The nocturia definition was recently updated by the International Continence Society (see the article by Hashim et al<sup>4</sup>) as: The number of times urine is passed during the main sleep period. Having woken to pass urine for the first time, each urination must be followed by sleep or the intention to sleep. This should be quantified using a bladder diary.



## References

1. van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):179-183.
2. Bosch JLHR, Weiss JP. The prevalence and causes of nocturia. *J Urol*. 2013;189(1 Suppl):S86-S92.
3. Everaert K, Hervé F, Bower W, et al. How can we develop a more clinically useful and robust algorithm for diagnosing and treating nocturia? ICI-RS 2017. *Neurourol Urodyn*. 2018;37:S46-S59.
4. Hashim H, Blanker MH, Drake MJ, et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function [published online ahead of print January 15, 2019]. *Neurourology and Urodynamics*. <https://doi.org/10.1002/nau.23917>
5. Weiss JP, van Kerrebroeck PEV, Klein BM, Nørgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. *J Urol*. 2011;186(4): 1358-1363.
6. Oelke M, Anderson P, Wood R, Holm-Larsen T. Nocturia is often inadequately assessed, diagnosed and treated by physicians: results of an observational, real-life practice database containing 8659 European and US-American patients. *Int J Clin Pract*. 2016;70(11):940-949.
7. Sakalis VI, Karavitakis M, Bedretdinova D, et al. Medical treatment of nocturia in men with lower urinary tract symptoms: systematic review by the European Association of Urology Guidelines Panel for male lower urinary tract symptoms. *Eur Urol*. 2017;72(5):757-769.
8. Callréus T. Use of desmopressin in elderly patients in Denmark. *Pharmacoepidemiol Drug Saf*. 2007;16(9):995-998.
9. Juul KV, Malmberg A, van der Meulen E, Walle JV, Nørgaard JP. Low-dose desmopressin combined with serum sodium monitoring can prevent clinically significant hyponatraemia in patients treated for nocturia. *BJU Int*. 2017;119(5):776-784.
10. Kaminetsky J, Fein S, Dmochowski R, et al. Efficacy and safety of SER120 nasal spray in nocturia patients pooled analysis of 2 randomized, double-blind, placebo-controlled phase 3 trials. *J Urol*. 2018;200:604-611.
11. Bower WF, Rose GE, Ervin CF, Goldin J, Whishaw DM, Khan F. TANGO - a screening tool to identify comorbidities on the causal pathway of nocturia. *BJU Int*. 2017;119(6):933-941.
12. Nambiar AK, Bosch R, Cruz F, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. *Eur Urol*. 2018;73(4):596-609.
13. van Haarst EP, Bosch JLHR. The optimal duration of frequency-volume charts related to compliance and reliability. *Neurourol Urodyn*. 2014;33(3):296-301.
14. Oelke M, De Wachter S, Drake MJ, et al. A practical approach to the management of nocturia. *Int J Clin Pract*. 2017;71(11):e13027.
15. Burton C, Weiss JP, Parsons M, Blaivas JG, Coats AC. Reference values for the Nocturnal Bladder Capacity Index. *Neurourol Urodyn*. 2011;30(1):52-57.
16. Bosch J, Everaert K, Weiss JP, et al. Would a new definition and classification of nocturia and nocturnal polyuria improve our management of patients? ICI-RS 2014. *Neurourol Urodyn*. 2016;35(2):283-287.
17. Olesen TK, Denys MA, Vande Walle J, Everaert K. Systematic review of proposed definitions of nocturnal polyuria and population-based evidence of their diagnostic accuracy. *Acta Clin Belg*. 2018;73:268-274.
18. Viaene A, Denys M-A, Goessaert A-S, et al. Evaluation of the occurrence and diagnose definitions for Nocturnal Polyuria in Spinal Cord Injured patients during rehabilitation [published online ahead of print November 3, 2017] *Eur J Phys Rehabil Med*. <http://www.ncbi.nlm.nih.gov/pubmed/29099160>
19. Goessaert AS, Krott L, Hoebeke P, Vande Walle J, Everaert K. Diagnosing the pathophysiologic mechanisms of nocturnal polyuria. *Eur Urol*. 2015;67(2):283-288.
20. Denys MA, Decalf V, Kumps C, Petrovic M, Goessaert AS, Everaert K. Pathophysiology of nocturnal lower urinary tract symptoms in older patients with urinary incontinence. *Int J Urol*. 2017;24(11):808-815.
21. Nørgaard JP, Hashim H, Malmberg L, Robinson D. Antidiuresis therapy: mechanism of action and clinical implications. *Neurourol Urodyn*. 2007;26(7):1008-1013.
22. Natsume O. A clinical investigation of nocturnal polyuria in patients with nocturia: a diurnal variation in arginine vasopressin secretion and its relevance to mean blood pressure. *J Urol*. 2006;176(2):660-664.
23. Asplund R, Åberg H. Diurnal variation in the levels of



antidiuretic hormone in the elderly. *J Intern Med.* 1991;229(2):131-134. 24. Graugaard-Jensen C, Hvistendahl GM, Frøkiaer J, Bie P, Djurhuus JC. Urinary concentration does not exclusively rely on plasma vasopressin. A study between genders. *Gender and diurnal urine regulation. Acta Physiol.* 2014;212(1):97-105. 25. Stachenfeld NS, Splenser AE, Calzone WL, Taylor MP, Keefe DL. Sex differences in osmotic regulation of AVP and renal sodium handling. *J Appl Physiol.* 2001;91(4):1893-1901. 26. Hanna-Mitchell AT, Robinson D, Cardozo L, Everaert K, Petkov GV. Do we need to know more about the effects of hormones on lower urinary tract dysfunction? ICI-RS 2014. *Neurourol Urodyn.* 2016;35(2):299-303. 27. National Institute for Health and Care Excellence. Menopause: diagnosis and management: guidance and guidelines. NICE; 2015. 28. Kamperis K, Hagstroem S, Radvanska E, Rittig S, Djurhuus JC. Excess diuresis and natriuresis during acute sleep deprivation in healthy adults. *Am J Physiol Renal Physiol.* 2010;299(2): F404-F411. 29. Fantus RJ, Packiam VT, Wang CH, Erickson BA, Helfand BT. The relationship between sleep disorders and lower urinary tract symptoms: results from the NHANES. *J Urol.* 2018;200:161-166. 30. Liu F, Zhang H, Liu Y, et al. Sleep Duration interacts with lifestyle risk factors and health status to alter risk of all-cause mortality: the rural Chinese cohort study. *J Clin Sleep Med.* 2018;14(5):857-865. 31. Cappuccio FP, Miller MA. Sleep and cardio-metabolic disease. *Curr Cardiol Rep.* 2017;19(11):110. 32. Cappuccio FP, D'elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep.* 2010;33(5):585-592. 33. Tikkinen KAO, Auvinen A, Johnson TM, et al. A systematic evaluation of factors associated with nocturia--the population- based FINNO study. *Am J Epidemiol.* 2009;170(3):361-368. 34. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213. 35. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999;131(7):485-491. 36. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology.* 2008;108(5):812-821. 37. Triarhou LC. Dopamine and Parkinson's disease. In: Madame Curie bioscience database. Austin, TX: Landes Bioscience; 2000-2013. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK6271/> 38. Connor JR, Wang XS, Allen RP, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain.* 2009;132(9):2403-2412. 39. Volkow ND, Tomasi D, Wang GJ, et al. Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. *J Neurosci.* 2012;32(19):6711-6717. 40. Batla A, Phé V, De Min L, Panicker JN. Nocturia in Parkinson's disease: why does it occur and how to manage?. *Mov Disord Clin Pract.* 2016;3(5):443-451. 41. Suchowersky O, Furtado S, Rohs G. Beneficial effect of intranasal desmopressin for nocturnal polyuria in Parkinson's disease. *Mov Disord.* 1995;10(3):337-340. 42. Denys MA, Cherian J, Rahnema'i MS, et al. ICI-RS 2015-Is a better understanding of sleep the key in managing nocturia. *Neurourol Urodyn.* 2018;37:2048-2052. 43. Romain J, Torny F, Dumas JP, Gamé X, Descazeaud A. Is nocturnal polyuria more frequent among patients with Parkinson's disease? *Prog Urol.* 2015;25(6):312-317. 44. Obayashi K, Saeki K, Kurumatani N. Independent associations between nocturia and nighttime blood pressure/dipping in elderly individuals: the HEIJO-KYO cohort. *J Am Geriatr Soc.* 2015;63(4):733-738. 45. Takayama M, Omori S, Iwasaki K, et al. Relationship between nocturnal polyuria and non-dipping blood pressure in male patients with lower urinary tract symptoms [published online ahead of print May 29, 2018]. *Low Urin Tract Symptoms.* <http://doi.wiley.com/10.1111/luts.12225> 46. Kahraman A, Dursun H, Hatipoglu S, et al. Non-dipping phenomenon in children with monosymptomatic nocturnal enuresis. *Pediatr Nephrol.* 2013;28(7):1099-1103. 47. Birkenhäger AM, van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. *Neth J Med.* 2007;65(4):127-131. 48. Stout N, Partsch H, Szolnoky G, et al. Chronic edema of the lower extremities: international consensus recommendations for compression therapy clinical research trials. *Int Angiol.* 2012;31(4):316-329.

49. Traves KP, Studdiford JS, Pickle S, Tully AS. Edema: diagnosis and management. *Am Fam Physician*. 2013;88(2):102-110. 50. O'Brien JG, Chennubhotla SA, Chennubhotla RV. Treatment of edema. *Am Fam Physician*. 2005;71(11):2111-2117. 51. Ely JW, Osheroff JA, Chambliss ML, Ebell MH. Approach to leg edema of unclear etiology. *J Am Board Fam Med*. 2006;19(2): 148-160. 52. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Rev Esp Cardiol*. 2016;69(12):1167. 53. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381. 54. Aoki Y, Yokoyama O. Metabolic syndrome and nocturia. *Low Urin Tract Symptoms*. 2012;4(s1):11-15. 55. Denys MA, Anding R, Tubaro A, Abrams P, Everaert K. Lower urinary tract symptoms and metabolic disorders: ICI-RS 2014. *Neurourol Urodyn*. 2016;35(2):278-282. 56. Stegenga H, Haines A, Jones K, Wilding J, Guideline Development Group. Identification, assessment, and management of overweight and obesity: summary of updated NICE guidance. *BMJ*. 2014;349: g6608. <http://www.ncbi.nlm.nih.gov/pubmed/25430558> 57. Garvey WT, Mechanick JL, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. *Endocr Pract*. 2016;22(Suppl 3):1-203. 58. Shamseddin MK, Parfrey PS. Mechanisms of the cardiorenal syndromes. *Nat Rev Nephrol*. 2009;5(11):641-649. 59. Hirayama A, Torimoto K, Yamada A, et al. Relationship between nocturnal urine volume, leg edema, and urinary antidiuretic hormone in older men. *Urology*. 2011;77(6):1426-1431. 60. Torimoto K, Hirayama A, Samma S, Yoshida K, Fujimoto K, Hirao Y. The relationship between nocturnal polyuria and the distribution of body fluid: assessment by bioelectric impedance analysis. *J Urol*. 2009;181(1):219-224. 61. Fabiani M, Saponara M, eds. *Diagnosis and therapy of snoring and OSAS*. The Hague, The Netherlands: Kugler Publications; 2000:1-4. 62. Dehoorne JL, Raes AM, van Laecke E, Hoebeke P, Vande Walle JG. Desmopressin resistant nocturnal polyuria secondary to increased nocturnal osmotic excretion. *J Urol*. 2006;176(2):749-753. 63. Vande Walle J, Vande Walle C, Van Sintjan P, et al. Nocturnal polyuria is related to 24-hour diuresis and osmotic excretion in an enuresis population referred to a tertiary center. *J Urol*. 2007;178(6):2630-2634. 64. DeSalvo KB, Olson R, Casavale KO. Dietary guidelines for Americans. *JAMA*. 2016;315(5):457-458. <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2015.18396> 65. Luft FC. Calcium-channel-blocking drugs and renal sodium excretion. *Am J Nephrol*. 1987;7(Suppl. 1):39-43. 66. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis*. 2008;52(1):144-153. 67. Andersson KE. The pharmacological treatment of nocturia. *BJU Int*. 2002;90(Suppl 3):25-27. 68. Robinson AG. DDAVP in the treatment of central diabetes insipidus. *N Engl J Med*. 1976;294(10):507-511. 69. Gudina EK, Ali K, Workicho A. Hyponatremia in patients hospitalized with heart failure: a condition often overlooked in low-income settings. *Int J Gen Med*. 2016;9:267-273. 70. Robinson D, Hanna-Mitchell A, Rantell A, Thiagamoorthy G, Cardozo L. Are we justified in suggesting change to caffeine, alcohol, and carbonated drink intake in lower urinary tract disease? Report from the ICI-RS 2015. *Neurourol Urodyn*. 2017;36(4): 876-881. 71. Sothorn RB, Vesely DL, Kanabrocki EL, et al. Circadian relationships between circulating atrial natriuretic peptides and serum sodium and chloride in healthy humans. *Am J Nephrol*. 1996;16(6):462-470. 72. Dumoulin C, Hunter KF, Moore K, et al. Conservative management for female urinary incontinence and pelvic organ prolapse review 2013: summary of the 5th International Consultation on Incontinence. *Neurourol Urodyn*. 2016;35(1):15-20. 73. Liu J, Sharma N, Zheng W, et al. Sex differences in vasopressin V2 receptor expression and vasopressin-induced antidiuresis. *Am J Physiol Renal Physiol*. 2011;300(2):F433-F440. 74. Juul KV, Klein BM,

Sandström R, Erichsen L, Nørgaard JP. Gender difference in antidiuretic response to desmopressin. *Am J Physiol Renal Physiol*. 2011;300(5):F1116-F1122. 75. Yamaguchi O, Nishizawa O, Juul KV, Nørgaard JP. Gender difference in efficacy and dose response in Japanese patients with nocturia treated with four different doses of desmopressin orally disintegrating tablet in a randomized, placebo-controlled trial. *BJU Int*. 2013;111(3):474-484. 76. Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature*. 2005;434(7031):400-404. 77. George E, Burke W, Hou J, et al. Measurement and validation of frailty as a predictor of outcomes in women undergoing major gynecologic surgery. *BJOG*. 2016;123(3):455-461. 78. Cesari M, Abellan Van Kan G, Ariogul S, et al. The European Union Geriatric Medicine Society (EUGMS) working group on frailty in older persons. *J Frailty Aging*. 2013;2(3):118-120. 79. Goessaert A-S, Everaert K, Hoebeke P, Vande Walle J. Pharmacokinetics and pharmacodynamics of the oral disintegrating tablet of desmopressin in adults with nocturnal polyuria: a pilot study. *Adv Ther*. 2015;32(9):799-808.